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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/709,577	05/14/2004	Itzhak Bentwich	050992.0202.02USCP	3576
37808	7590	10/24/2008		
ROSETTA-GENOMICS c/o PSWS 700 W. 47TH STREET SUITE 1000 KANSAS CITY, MO 64112			EXAMINER WOLLENBERGER, LOUIS V	
			ART UNIT 1635	PAPER NUMBER
			MAIL DATE 10/24/2008	DELIVERY MODE PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/709,577	Applicant(s) BENTWICH ET AL.	
	Examiner Louis Wollenberger	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 04 August 2008 and 23 September 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 25-27, 29-31 and 33 is/are pending in the application.
- 4a) Of the above claim(s) 26, 29, 30 and 33 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 25, 27 and 31 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>8/4/08</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/4/08 has been entered. Applicant's supplemental response filed 9/23/08 is also acknowledged and is considered herein.

Status of Application/Amendment/Claims

Applicant's response filed 8/4/08 and 9/23/08 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 6/17/08 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 8/4/08, claims 25-27, 29-31, and 33 are pending in the application. Claims 26, 29, 30, and 33 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 25, 27, and 31, drawn to an isolated nucleic acid consisting of SEQ ID NO: 7,002,375 or SEQ ID NO:6816665.

Claim Objections

Claim 31 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

The instant claim is drawn to vectors comprising the isolated nucleic acid of claim 25 and 27, respectively. The use of open “comprising” language in dependent claim 31 suggests the vectors claimed therein may include, for example, SEQ ID NO:7002375 or 6816665 as well as additional unrecited DNA. However, the language used in claims 25 and 27 to define the isolated nucleic acids, while not entirely clear, suggests claims 25 and 27 exclude any additional unrecited elements (MPEP 2111.03).

Notwithstanding the ambiguity of the language used in claims 25 and 27, for purposes of this examination, claims 25 and 27 are interpreted as being closed, limited to the sequences consisting of (a), (b), or (c)---nothing less and nothing more. Accordingly, the use of open ended “comprising” language in claim 31, without anything more, improperly broadens the claim to include vectors comprising long stretches of DNA encoding the nucleic acid of (a) along with any other additional RNA sequences.

MPEP 608.01(n) states that the test as to whether a claim is a proper dependent claim is that it shall include every limitation of the claim from which it depends (35 U.S.C. 112, fourth paragraph) or in other words that it shall not conceivably be infringed by anything which would not also infringe the basic claim. As shown by the art rejection below under 35 USC 102, claims

26 and 32 violate this precept inasmuch as they are anticipated by a prior art vector that does not also anticipate the claims from which they depend

Correction is required.

Claim Rejections - 35 USC § 101 and 112, First Paragraph— maintained in part

Claims 25, 27, and 31 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by a credible asserted utility for the reasons set forth in the Action mailed 9/20/07 and 6/17/08.

Response to Arguments/Declaration under 37 CFR §1.132

Though not clearly stated in the submission or in Applicant's remarks, the Declaration by Ayelet Chajut, filed 9/23/08, is considered to represent and be in compliance with a declaration under 37 CFR 1.132, by which Applicant may submit evidence not currently of record.

The Declaration under 37 CFR 1.132 filed 9/23/08 is sufficient to overcome the rejection of claims 25, 27, and 31 in part. Specifically, the evidence in the Declaration is sufficient to overcome the utility rejection with regard to the 22-nucleotide, bioinformatically predicted miRNA encoded by SEQ ID NO:7002375; the DNA sequence encoding said miRNA; the length-identical complement of said miRNA and DNA; and the vector comprising an insert that is identical in length to said DNA and no other inserts or sequences contiguously encoded with said DNA.

Accordingly, the Declaration is sufficient to show credible utility for the mature, processed 22-nucleotide miRNA consisting of the RNA sequence encoded by the sequence consisting of SEQ ID NO:7002375.

The rejection is maintained, however, with respect to the pre-processed, bioinformatically predicted miRNA-like hairpin consisting of the sequence encoded by SEQ ID NO:6816665, as well as all vectors thereof. The rejection is further maintained as applied to sequences that are 80% identical to SEQ ID NO: 7002375 or SEQ ID NO:6816665, as well as any complements thereof with less than 100% identity to SEQ ID NO:7002375. The evidence submitted by affidavit is not commensurate in scope with claims (MPEP 716.02(d) and 2107.02). The evidence is more narrowly drawn to the activity of the claimed 22-mer, SEQ ID NO:7002375 and does not address the proposed activities of all sequences 80% identical to the 22-mer or the complements of such sequences or the vectors comprising said sequences. Moreover, there is still sufficient reason, based on the extrinsic evidence cited to date, to doubt whether the bioinformatically predicted hairpin molecule corresponding to SEQ ID NO:6816665 gives rise to SEQ ID NO:7002375 in the cell, or whether SEQ ID NO:6816665 has substantially the same activity as SEQ ID NO:7002375. While SEQ ID NO:6816665 may reasonably give rise to sequences that are 80% identical to SEQ ID NO: 7002375 the evidence submitted does not establish a nexus between these sequences and the MAPKAPK2 expression or activity.

As each claim continues to recite elements that lack utility for the reasons set forth in the earlier Action, each claim remains rejected herein. Amending the claims to remove these elements would overcome the rejection in its entirety.

Claims 25, 27, and 31 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific, substantial, and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 25 and 31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The scope and meaning of the limitation "a sequence at least 80% identical to (a) or (b)" is unclear. Neither the claims nor the specification define the method by which percent identity is calculated. Given the voluminous nature of the application and the fact that no pre-grant publication currently exists the Examiner is unable to readily locate any disclosure therein clearly describing how percent identity is to be defined. Thus, it is unclear whether the claims read on sequences that are shorter or longer than the instantly claimed 22-mer that share partial identity therewith.

For purposes of this examination the claims are interpreted broadly to include any sequence of any length comprising at least 80% of the sequence corresponding to SEQ ID NO:7002375.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –


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(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 25 is rejected under 35 U.S.C. 102(b) as being anticipated by GenBank Accession No. BD247503.1 "Maize DNA ligase I orthologue and uses thereof", as published online 17 July 2003, retrieved from the Nation Center for Biotechnology Information [online] on October 22, 2008 at ncbi.nlm.nih.gov/entrez.

As shown by the alignment below, an isolated nucleic acid sequence comprising at least 80% of instant SEQ ID NO:7002375 was known in the prior art. See GenBank Acc. No. BD247503.

Accordingly, the sequences claimed in claim 25, part b, are anticipated by the prior art.

```
>  dbj|BD247503.1| Maize DNA ligase I orthologue and uses thereof
Length=2941

Score = 32.2 bits (16), Expect = 3.6
Identities = 19/20 (95%), Gaps = 0/20 (0%)
Strand=Plus/Plus

Query 1      ACATACACGGGAAACCTCTT  20
          ||||| |||||
Sbjct 2036   ACATAAACGGGAAACCTCTT  2055

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Claims 25 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by GenBank Accession No. AC_096504.7 "Rattus norvegicus clone CH230-167O14, WORKING DRAFT SEQUENCE", as published online 10 May 2003, retrieved from the Nation Center for Biotechnology Information [online] on October 22, 2008 at ncbi.nlm.nih.gov/entrez, as evidenced by

1) Kim et al. (1996) “Construction and characterization of a human bacterial artificial chromosome library” *Genomics* 34:213-218, teaching the use of bacterial artificial chromosomes for the propagation and sequence of human genomic DNA; and

2) The International Human Genome Sequencing Consortium (2001) “Initial sequencing and analysis of the human genome” *Nature* 409:860-921.

As explained above in the Claim Objections, claims 25 and 31 read on vectors comprising SEQ ID NO:7002375.

As shown by GenBank Accession No. AC_096504.7, and the alignment below, and as evidenced by Kim et al. and The International Human Genome Sequencing Consortium, a bacterial artificial chromosome vector containing a DNA encoding instant SEQ ID NO: 7002375 was known in the prior art.

GenBank Accession No. AC_096504.7 states the *Rattus norvegicus* clone CH230-167O14 sequence is a combination of BAC based reads and whole genome shotgun sequencing.

As evidenced by Kim et al. and The International Human Genome Sequencing Consortium, it was universally recognized that chromosome clones, for genomic sequencing, were generally maintained and propagated as BACs.

Kim et al. taught that bacterial artificial chromosomes are cloning vectors that allow for the stable propagation and sequencing of large DNA inserts, such as portions of human chromosomes.

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The International Human Genome Sequencing Consortium used BACs as their source of human chromosomal DNA for physical mapping and sequencing. See for example Fig. 2, page 863.

Accordingly, there is sufficient evidence to show that all and/or portions of GenBank Accession No. AC096504.7 were made and used as bacterial artificial chromosome vectors more than a year prior to the filing date of the instant application.

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> gb|AC096504.7| Rattus norvegicus clone CH230-167O14, WORKING DRAFT
SEQUENCE,
4 unordered pieces
Length=253092

Score = 44.1 bits (22), Expect = 0.005
Identities = 22/22 (100%), Gaps = 0/22 (0%)
Strand=Plus/Plus

Query 1          ACATACACGGGAAACCTCTTTT  22
          |||||
Sbjct  213238 ACATACACGGGAAACCTCTTTT  213259

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Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claim 25 is rejected under 35 U.S.C. 103(a) as being unpatentable over GenBank

Accession No. AC_096504.7 "Rattus norvegicus clone CH230-167O14, WORKING DRAFT SEQUENCE ", as published online 10 May 2003, retrieved from the Nation Center for

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Biotechnology Information [online] on October 22, 2008 at ncbi.nlm.nih.gov/entrez, as evidenced by

1) Kim et al. (1996) “Construction and characterization of a human bacterial artificial chromosome library” *Genomics* 34:213-218, teaching the use of bacterial artificial chromosomes for the propagation and sequence of human genomic DNA; and

2) The International Human Genome Sequencing Consortium (2001) “Initial sequencing and analysis of the human genome” *Nature* 409:860-921.

in view of Buck et al (BioTechniques 27: 528-536, 1999).

Claim interpretation:

Broadest reasonable interpretation of the nucleic acids defined in parts a, c, and d of claim 25 includes DNA probes and sequencing primers. SEQ ID NO:7002375 is a 22-nucleotide DNA.

The rejection:

The following rejection applies to parts a, c, and d of claim 25.

GenBank Accession No. AC_096504.7 taught a bacterial artificial chromosome vector comprising at least a portion of a rat chromosome that includes nucleotides that are identical and complementary to instant SEQ ID NO: 7002375. Accordingly GenBank Accession No.

AC_011453 taught a vector that comprised a DNA sequence complementary to instant SEQ ID NO: 7002375.

GenBank Accession No. AC_096504.7 did not teach an isolated nucleic acid consisting of SEQ ID NO: 7002375 or identical-length complements of SEQ ID NO:7002375.

However, it is clear that it was obvious to those of ordinary skill in the art that sequencing primers were required in order to obtain the sequence disclosed in GenBank Accession No. AC_096504.7. It is considered obvious for the reasons set forth below to make primers of the same length of SEQ ID NO: 7002375, and further, these primers can be considered to be probes.

Buck analyzed the effect of primer design strategy on the performance of DNA sequencing primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that every single primer worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, every single control primer functioned as well (see page 533, column 1). Buck expressly states “The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2).” Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

It would have been obvious to one of ordinary skill in the art at the time of the invention to synthesize a DNA complement identical or complementary to instant SEQ ID NO: 7002375 (a 22-mer) as a primer in the process of determining the sequence disclosed in GenBank Accession

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No. AC_096504.7. In view of the teachings of Buck, sequencing primers can be synthesized essentially anywhere along a given sequence of interest, and under optimal conditions they will reasonably be expected to perform adequately to yield sequence data. See page 533, left column, first full paragraph, and paragraph bridging pages 535 and 536. It would have been obvious to select a primer length of 22 nucleotides because those of ordinary skill normally use sequencing primers of 19-24 nucleotides in length (see Buck abstract.). Accordingly, any 22 nucleotide fragment represented in either strand of the vector of GenBank AC_096504.7, including those that would have been at least 80% identical to instant SEQ ID NO:7002375, is considered to be obvious.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis Wollenberger whose telephone number is (571)272-8144. The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571)272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Louis Wollenberger/
Examiner, Art Unit 1635
October 22, 2008